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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,167	01/08/2002	James Gordon Adamson	6704-268	8982
1059	7590	02/12/2004	EXAMINER	
BERESKIN AND PARR SCOTIA PLAZA 40 KING STREET WEST-SUITE 4000 BOX 401 TORONTO, ON M5H 3Y2 CANADA			KWON, BRIAN YONG S	
			ART UNIT	PAPER NUMBER
			1614	

DATE MAILED: 02/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/926,167

Applicant(s)

ADAMSON ET AL.

Examiner

Brian S Kwon

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 October 2003.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 7, 8 and 10-45 is/are pending in the application.
4a) Of the above claim(s) 25-35 is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-4, 7-8, 10-24 and 36-45 is/are rejected.
7) ☒ Claim(s) 36-41 is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Summary of Action

- I. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).
- II. The objection of claim 7 will not be maintained in light of the amendment.
- III. The rejection of claim 1-4 and 7 under 35 USC 112, first paragraph, will not be maintained in light of the amendment.
- IV. The rejection of claims 13-22 under 35 USC 112, second paragraph, will not be maintained in light of the amendment.
- V. The rejection of claims 1-17 under 35 USC 102(a) will not be maintained in light of the amendment/remarks.
- VI. The rejection of claims 11-12 and 23 under 35 USC 112, second paragraph, will be maintained for the reason of the record.
- VII. The rejection of claims 1-3, 13-15 and 20 under 35 USC 102(b) will be maintained for the reason of the record.
- VIII. The rejection of claims 4, 7-8, 10-12, 16-19, 21-24 under 35 USC 103(a) will be maintained for the reason of the record.
- IX. Applicant's amendment necessitated a new ground of rejection(s) in this Office Action.

Status of Application

1. By Amendment filed October 23, 2003, Claims 5-6 and 9 have been cancelled; Claims 1, 3, 4, 8, 10-24 have been amended; and Claims 4-5 and 36-43 have been newly added.

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2. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 6, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 have been renumbered as 4, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 respectively. Also, newly added claims 4 and 5 have been renumbered as 44 and 45 respectively.

Response to Amendment

3. The amendment filed October 23, 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "P50 of the conjugate".

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

4. Claim 43 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 43 recites the limitation "the P50 of the conjugate" in claim 1. There is insufficient antecedent basis for this limitation in the claim. Furthermore, it is not clear at all what is meant by "the P50 of the conjugate is 40".

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5. Claims 11-12 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This rejection is analogous to the original rejection. Claim 11 recites "R4 is a direct bond or C1-8 alkyl chain". There is no antecedent basis for this limitation in the claim. If this is still typographical error, applicant is requested to change "R4" to "R'4". Similarly, in claim 23, there is no antecedent basis for "R4" in the claim 22 which further depends on claim 10.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-3, 13-15 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Kluger (WO 97/00236).

This rejection is analogous to the original rejection.

7. Claim 45 is rejected under 35 U.S.C. 102(b) as being anticipated by Levy et al. (US 5780060).

Levy teaches a microcapsules comprising flavonoids (i.e., flavonone) interfacially crosslinked with a diacid halide crosslinking agent, co-crosslinked with protein (i.e., hemoglobin), see claims 1-7).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 4, 7-8, 10-12, 16-19, 21-24 and 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hsia (US 5789376 A) in view of Beach et al. (Archives of Biochemistry and Biophysics, 1992, abstract, 297 (2), 258-64).

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Hsia discloses a composition comprising stabilized hemoglobin covalently bound to antioxidant such as a nitroxide, wherein the hemoglobin is cross-linked using polyvalent aldehyde derived from a ring-opened cyclic sugar (e.g., o-raffinose), see claims.

Beach teaches the use of tocopherol analogs (e.g., Trolox) and nitroxides as an antioxidant. The reference teaches that chromanol is the most active antioxidant among other antioxidants.

The teaching of Hsia differs from the claimed invention in the use of other antioxidant, namely 2,5,7,8-tetramethyl-2-carboxy-chroman-6-ol (Trolox) in preparing hemoglobin conjugate. To incorporate such teaching into the teaching of Hsia, would have been obvious in view of Beach who teaches or suggests the use of chromanol based antioxidant such as Trolox as the most active antioxidant. One having ordinary skill in the art would have expected that Trolox would have similar properties as an antioxidant. Further, one having ordinary skill in the art would have been motivated to substitute nitroxide with Trolox having the most active antioxidant property, with the reasonable expectation of success, to provide a hemoglobin composition with enhanced oxygen-transferring function (as blood substitutes) while oxidative stress and oxygen-related toxicity is greatly reduced.

With respect to "Hb:antioxidant ratio is 1:1-1:3.7" in newly added claim 42, optimization of amounts of known active and inactive ingredients in a composition is considered within the level of the skill artisan, and the artisan would be motivated to determine optimum amounts having maximum therapeutic effects of the drug or composition. Therefore, the reference makes obvious the claimed invention.

Response to Arguments

Applicant's arguments filed October 23, 2003 have been fully considered but they are not persuasive.

9. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

10. Applicant alleges that (i) there is no specific mention in Kluger of using the cross-linker to link antioxidants per se to hemoglobin with the said activity, purpose and result of the present invention; (ii) the compounds mentioned in Kluger are not generally known by a person skilled in the art to be used as an antioxidant; (iii) Kluger does not teach a hemoglobin conjugate having an antioxidant and wherein the hemoglobin retains its oxygen transport capabilities; (iv) Kluger does not teach directly linking an antioxidant or other compound to the hemoglobin (e.g., not through an intramolecular crosslinker). The examiner disagrees.

In response to "there is no specific mention in Kluger of using the cross-linker to link antioxidants per se to hemoglobin with the said activity, purpose and result of the present invention" and "Kluger does not teach...the hemoglobin retains its oxygen transport capabilities", claims to a composition possessing a particular property or characteristic are still properly rejected by a reference to the same composition, even if the reference does not address or acknowledge the property.

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In response to “the compounds mentioned in Kluger are not generally known by a person skilled in the art to be used as an antioxidant”, since the referenced compound falls within the definition of the claimed antioxidant, where “the antioxidant is a phenolic compound containing one or more groups of the formula”, “non-enzymatic phenolic compounds” or “a substituted phenolic”, the reference anticipates the claimed invention.

In response to “Kluger does not teach directly linking an antioxidant or other compound to the hemoglobin (e.g., not through an intramolecular crosslinker)”, there is no where in the instantly rejected claims that linking an antioxidant or other compound to the hemoglobin must be through an intramolecular crosslinker. Therefore, the referenced teaching of hemoglobin-biomolecule (e.g., hormones) conjugate crosslinked by the crosslinking agent anticipates the claimed invention.

11. Applicant alleges that (a) Hsia does not disclose a hemoglobin conjugated to an antioxidant of the present invention, a “phenolic” antioxidant; (b) Hsia fails to suggest that any other anti-oxidants should be used or that by binding an antioxidant to the hemoglobin one obtains a synergistic effect; (c) no where in Beech suggest to bind the TROLOX to hemoglobin to ameliorate its antioxidant activity.

In response to “Hsia does not disclose a hemoglobin conjugated to the phenolic antioxidant”, as discussed above, the referenced compound falls within the definition of the claimed antioxidant, where “the antioxidant is a phenolic compound containing one or more groups of the formula”, “non-enzymatic phenolic compounds” or “a substituted phenolic”, therefore, the reference makes obvious the claimed invention.

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In respect to the claimed synergistic effect (see Example 9) and, applicant's showing of unexpected superior result is found persuasive.

In response to "no where in Beech suggest to bind the TROLOX to hemoglobin to ameliorate its antioxidant activity", although the examiner disagrees with this argument, the examiner withdraws from this rejection in view of the unexpected superior results shown in Example 9.

Allowable Subject Matter

12. A composition comprising Hemoglobin-Trolox conjugate or polyOR-Hemoglobin-Trolox appears to be allowable over the prior art. The primary reason for indicating allowable subject matter is applicant's showing of unexpected results in Hemoglobin-Trolox complex (Example 9).

Conclusion

13. Claims 36-41 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (703) 308-5377. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (703) 308-4725. The fax number for this Group is (703) 308-4556.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Brian Kwon

**ZOHREH FAY
PRIMARY EXAMINER
GROUP 1600**

A handwritten signature in black ink, appearing to read 'Zohreh Fay', is written below the printed name.